REMARKS

Claims 21 and 35-37 are pending. Claim 21 is currently amended so that in step (vi) the phrase "improves the response to glucose" is amended to specifically refer to an improvement in the amount of insulin released (i.e. increase in the amount of insulin released). Support for the amendment is found in paragraph **[0015]** on page 4 and in paragraph **[0033]** on page 7:

[0015] In another embodiment, the methods of the invention can further comprise administering the agent to a diabetic or pre-diabetic animal; determining the sensitivity of insulin secretion to glucose levels in the animal; and selecting a candidate agent that improves the sensitivity of insulin secretion in response to glucose. The step of determining the sensitivity of the animal may comprises, e.g., determining the amount of insulin released from pancreatic tissue in response to glucose.

[0033] Typically, a response to blood glucose levels is measured by assessing the level of insulin secretion. The term "sensitivity of glucose-stimulated insulin secretion" or "sensitivity of insulin secretion to glucose levels" refers to the ability of pancreatic cells to release insulin in response to glucose levels. "Insensitive" in this context typically means that insulin secretion in response to normal, i.e., about 5.6 mM, or higher glucose levels is reduced in comparison to insulin secretion in normal, non-diabetic (lean) pancreatic cells.

Applicants respectfully requests reconsideration of the present application in view of the amendments and the reasons that follow.

The 35 USC § 103(a) rejection

Claims 21 and 35-37 stand rejected under 35 USC § 103(a) over Meyers et al. (US 2002/0009779), Newgard et al. (US Patent 5,854,067), and Liang et al. (J. of Biological Chemistry, 1990 Vol. 265:16863-16866).

The rejection is respectfully traversed, as the references, alone or in combination, do not teach all of the claim limitations. As such, the obviousness rejection is in error. Specifically, the references do not teach or suggest step (vi) of selecting an inhibitor that improves insulin release in response to glucose in a diabetic cell.

Claim 21, as amended, recites in steps (iii) and (vi) (emphasis added):

21. A method for identifying an agent for treating a **diabetic or pre-diabetic** individual having impaired glucose-induced insulin secretion, the method comprising the steps of:

(i) contacting a candidate agent with a polypeptide having glucose phosphorylating activity that comprises SEQ ID NO:2;

(ii) determining binding of the agent to the polypeptide, wherein determining binding of the agent to the polypeptide comprises determining the activity of the polypeptide;

(iii) selecting an agent that **decreases** the activity of the polypeptide;

(iv) administering the agent to a **diabetic or pre-diabetic** animal;

(v) determining the level of glucose-induced insulin secretion in the animal in response to glucose; and

(vi) selecting the agent that **improves insulin release** in response to glucose.

Applicants will address each reference for their teachings in this regard.

Meyers et al. (US 2002/0009779)

Meyers discloses 50365, a polypetide corresponding to SEQ ID NO:2. Meyers discloses in paragraph [0224] methods for screening compounds that modulates the activity of 50365. However, Meyers does not teach use of 50365 in a screening assay having the steps of testing and selecting an inhibitor that improves insulin release. Meyers also does not teach or suggest that inhibiting 50365 will lead to an increase in insulin release in response to glucose. Moreover, Meyers does not provide any teachings as to what role, if any, 50365 or other hexokinases play in diabetes.

Newgard et al. (US Patent 5,854,067)

Newgard states in column 2 lines 11-39 that insulin injection is the accepted method of treatment for insulin dependent diabetes mellitus and that the development of engineered insulin producing cells holds promise for cell-based therapy, but that such cells currently are not likely to secrete insulin at physiological glucose conditions. Engineered cells have an imbalance in the

glucokinase:hexokinase ratio and Newgard teaches ways to correct this imbalance by using hexokinase inhibitors. Notably, Newgard teaches that the hexokinases are to be inhibited to achieve a glucokinase:hexokinase ratio that more closely resembles that found in normal pancreatic cells (column 3 lines 38-49):

> In certain embodiments, particularly where the cell in question is an engineered cell designed to secrete insulin in response to glucose, other parameters may be applied in assessing useful levels of low K_m hexokinase inhibition. For example, it may be desired to determine the ratio of glucokinase to hexokinase (GK:HK ratio) and to monitor changes in this ratio as hexokinase is inhibited. *It will be understood that a cell in which this ratio is changed to reflect the ratio commonly observed in functional or natural pancreatic β cells, or in which the ratio is changed towards this, will be an advantageous engineered cell in the context of this invention.* (emphasis added)

However, Newgard does not teach that natural diabetic cells also have a similar imbalance in the glucokinase:hexokinase ratio. Newgard also does not teach that inhibiting hexokinases will be expected to cause diabetic cells to being to produce more insulin in response to glucose. Furthermore Newgard is silent on the role played by hexokinases in diabetes. Therefore Newgard does not cure the deficiency in Meyers for selecting a hexokinase inhibitor that will also *increase* insulin secretion in diabetic cells in response to glucose.

Liang et al. (J. of Biological Chemistry, 1990 Vol. 265:16863-16866)

Liang teaches in Figure 1 measurement of insulin secretion from islet cells that are challenged with glucose. As with Meyers and Newgard, Liang is silent on the role that glucokinase or other hexokinases plays in diabetes. What Liang does teach is that is that glucokinase is an essential enzyme in sensing glucose and triggering the release of insulin. Therefore the findings in Liang imply that if glucokinase were to be inhibited, it would no longer be able to release insulin in response to glucose. Accordingly, Liang does not cure the deficiency in Meyers for selecting a hexokinase inhibitor that will also *increase* insulin secretion in diabetic cells in response to glucose.

Present Application

The findings of the present application (see Figures 1-10) provide evidence of the role of hexokinase V in glucose induced insulin secretion. In particular, Figure 10 shows the unexpected finding that overexpression of hexokinase V results in a decrease in insulin secretion as a response to glucose stimulation. This result suggests that inhibition of hexokinase V in pancreatic cells can result in increased insulin secretion.

The cited references do not provide any rationale as to why one of skill in the art would want to inhibit a hexokinase in a diabetic cell, much less inhibiting hexokinase V of the pending claims. Moreover, the cited references do not teach or suggest that inhibiting hexokinase V will increase insulin release in diabetic cells in response to glucose. Consequently, there is no suggestion to arrive at the claimed assay to screen for agents having both of these limitations.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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